miR-10 Regulates the Angiogenic Behavior of Zebrafish and Human Endothelial Cells by Promoting VEGF Signaling.

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Public Summary:
Formation and remodeling of blood vessels during development and disease involves a precisely regulated network of attractants and repellants that is similar across species. Various signaling pathways control the behavior of endothelial cells—the cells that line the interior surface of blood vessels. The objective of this study is to identify microRNAs—small, non-coding RNAs that help control gene expression—that contribute to the regulation of new blood vessel formation. We show that a microRNA called miR-10 regulates the behavior of endothelial cells during blood vessel formation by encouraging signals that promote blood vessel growth. Genetic experiments in zebrafish revealed that miR-10 functions, in part, by directly regulating the level of a protein called FLT1, which inhibits the behavior of endothelial cells that promotes new blood vessel growth. The ability to regulate blood vessel growth is important for treating many diseases, including cancer.

Scientific Abstract:
Rationale: Formation and remodeling of the vasculature during development and disease involves a highly conserved and precisely regulated network of attractants and repellants. Various signaling pathways control the behavior of endothelial cells, but their post-transcriptional dose-titration by miRNAs is poorly understood. Objective: To identify miRNAs that regulate angiogenesis. Methods and Results: We show that the highly conserved microRNA family encoding miR-10 regulates the behavior of endothelial cells during angiogenesis by positively titrating pro-angiogenic signaling. Knockdown of miR-10 led to premature truncation of intersegmental vessel growth (ISV) in the trunk of zebrafish larvae, while overexpression of miR-10 promoted angiogenic behavior in zebrafish and cultured human umbilical venous endothelial cells (HUVECs). We found that miR-10 functions, in part, by directly regulating the level of fms-related tyrosine kinase 1 (FLT1), a cell-surface protein that sequesters VEGF, and its soluble splice variant sFLT1. The increase in FLT1/sFLT1 protein levels upon miR-10 knockdown in zebrafish and in HUVECs inhibited the angiogenic behavior of endothelial cells largely by antagonizing VEGF receptor-2 signaling. Conclusions: Our study provides insights into how FLT1 and VEGF receptor-2 signaling is titrated in a miRNA-mediated manner and establishes miR-10 as a potential new target for the selective modulation of angiogenesis.